HMG-CoA Reductase Inhibitors (Statins) – Safety Overview

Atorvastatin (Lipitor® – Pfizer)
Fluvastatin (Lescol® – Novartis, Lescol XL® – Novartis)
Lovastatin (Altoprev™ – Andrx, Mevacor® – Merck, generics)
Pravastatin (Pravachol® – Bristol-Myers Squibb, generics)
Rosuvastatin (Crestor® – AstraZeneca)
Simvastatin (Zocor® – Merck, generics)
AHFS 24:06 Antilipemic Agents

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Executive Summary

No controlled trials have evaluated comparative risk as a primary endpoint. Serious events are rare but include muscle toxicity, liver failure, and renal failure.

- Comparative Risk Of Skeletal Muscle Toxicity

  Myopathy and rhabdomyolysis have occurred with all the statins. There is no evidence that one statin is safer in this regard. Risk appears similar with all the available agents except rosuvastatin. Rosuvastatin may be more likely to cause myopathy or rhabdomyolysis, based on retrospective analyses which did not report whether equipotent doses were administered.

- Relationship Between Risk Of Skeletal Muscle Toxicity And Statin Dose

  Myopathy and rhabdomyolysis appear to be dose-related, although the exact risk is unknown for each agent and dose. Additional study is needed to quantify the specific relationship. Drug interactions that increase systemic statin exposure may increase risk of muscle toxicity.

- Comparative Risk Of Hepatotoxicity

  No clinical trials have evaluated the comparative risk of hepatotoxicity with the statins. The available evidence suggests that risk is similar with the available agents.

- Comparative Risk Of Renal Side Effects

  No trials have evaluated the comparative risk of renal toxicity with the statins. The available evidence suggests that risk is similar with the available agents, although the risk appeared higher with rosuvastatin in some retrospective analyses which did not specify doses used.

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Safety Overview

No controlled clinical trials have evaluated the comparative risk of adverse events with the statins as a primary endpoint. Common side effects of the statins include non-specific gastrointestinal (GI) complaints, headache, and rash.[1-8] Differences in adverse effect profiles between drugs may be due to pharmacokinetic differences between the agents. In theory, fluvastatin and rosuvastatin may induce fewer central nervous system (CNS) side effects such as headache, dizziness, and asthenia due to their low lipophilicity.[9, 10] However, no studies have demonstrated a difference in CNS adverse effects. Class effects include skeletal muscular myopathy, hepatic transaminase elevations, and non-specific gastrointestinal complaints.[2-8] Table 1 compares the relative frequency of adverse effects for the available statins.

A meta-analysis of 18 controlled trials attempted to quantify the comparative risk of adverse effects with atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin (Appendix B, Evidence Table 1).[11] The results are difficult to interpret because the investigators performed many two-agent comparisons. The analysis found that risk of any adverse effect with lovastatin was similar to each of the other agents. Atorvastatin was more likely to cause any adverse effect than fluvastatin, pravastatin, or simvastatin. Risk of any adverse effect with fluvastatin was similar to simvastatin, but less likely than pravastatin. Risk of any adverse effect was similar with pravastatin or simvastatin.[11] These results do not allow for any consistent ranking of adverse event risk.

A retrospective review of the FDA's adverse event reporting system attempted to evaluate the risk of adverse effects with the available agents, but made no statistical comparisons between the agents (Appendix B, Evidence Table 1).[12] The huge disparity in the number of reports suggests that cerivastatin may be more likely to cause adverse effects than the available statins, including any adverse effect, serious or fatal adverse effects, rhabdomyolysis, liver failure / hepatitis, or renal failure. Similar disparities suggest that rosuvastatin may be more likely to cause some adverse effects than the other statins, including any adverse effect, serious or fatal adverse effects, rhabdomyolysis, liver failure / hepatitis, or renal failure. Simvastatin may be more likely than the other agents to cause rhabdomyolysis or liver failure / hepatitis. The authors' assertion is that adverse effect reporting increased after cerivastatin's withdrawal.[12] However, this seems unlikely to account for the large difference in reports between the agents. If anything, the number of reports would be expected to increase dramatically for all the agents, rather than just for one or two statins.

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Table 1. Frequency (%) of Selected Adverse Effects with the Available Statins*[2-8, 13]

Adverse Reaction	Atorvastatin 10 – 80 mg (n = up to 2,502)	Fluvastatin IR 20 – 80 mg (n = up to 2,969)	Fluvastatin ER 80 mg (n = 912)	Lovastatin IR 20 – 80 mg (n = 6,582)	Lovastatin ER Dose not specified (n = 467)	Rosuvastatin 10 – 40 mg (n = up to 10,275)	Pravastatin 10 – 40 mg (n = up to 10,764)	Simvastatin 20 – 40 mg (n = up to 10,269)
Discontinued due to side effects	< 2	1	3.9	4.6	< 3	3.7	1.7	1.4 – 4.8
Gastrointestinal								
Abdominal pain/cramps	0 – 3.8	4.9	3.7	2 – 2.5		≥ 2	2.4 – 5.4	0.9 – 3.2
Constipation	0 – 2.5	3.1[14]	2.3[14]	2 – 3.5		≥ 2	1.2 – 4	2.3
Diarrhea	0 – 5.3	4.9	3.3	2.2 – 2.6	3	3.4	6.2	0.2 – 1.9
Dyspepsia	1.3 – 2.8	7.9	3.5	0.5 – 1.6		3.4	2.9 – 3.5	0.6 – 1.1
Flatulence	1.1 – 2.8	2.6	1.4	3.7 – 4.5		1 – 2	1.2 – 3.3	0.9 – 1.9
Increased hepatic transaminases (persisting above 3 times upper limit of normal)	0.2 – 2.3	0.2 – 4.9	1.9	0.1 – 1.9		0 – 0.4	≤ 1.2	0.4 – 1
Nausea/vomiting	≥ 2	3.2	2.5	1.9 – 2.5		3.4	1.6 – 7.3	0.4 – 1.3
Musculoskeletal								
Arthropathy			3.2					
Arthralgia	0 – 5.1	4[14]	1.3[14]	0.5 – 1	5	≥ 2	6	
Arthritis	≥ 2	2.1	1.3			≥ 2		
Back pain	0 – 3.8	5.7[14]	4.7[14]		5	2.6		
Localized pain				0.5 – 1	3	≥ 2	10	
Muscle cramps/pain	< 2			0.6 – 1.1			2	
Myalgia	0 – 5.6	5	3.8	1.8 – 3	3	2.8	1.4 – 2.7	1.2
Nervous System								
Asthenia	0 – 3.8			1.2 – 1.7	3	2.7	< 1	1.6
Dizziness	≥ 2	2.2[14]	1.9[14]	0.5 – 1.2	2	≥ 2	2.2 – 3.3	
Fatigue	Reported	2.7	1.6				3.4 – 3.8	
Headache	2.5 – 16.7	8.9	4.7	2.1 – 3.2	7	5.5	1.9 – 6.2	3.5
Insomnia	≥ 2	2.7	0.8	0.5 – 1		≥ 2	< 1	
Paresthesia	< 2			0.5 – 1		≥ 2	< 1	
Respiratory								
Bronchitis	≥ 2	1.8	2.6			≥ 2		
Common cold							7	
Cough		2.4[14]	1.9[14]			≥ 2	1 – 2.6	
Pharyngitis	0 – 2.5	3.8[14]	2.4[14]			9		
Rhinitis	≥ 2	4.7[14]	1.5[14]			2.2	4	
Sinusitis	0 – 6.4	2.6[14]	3.5[14]		4	2		
Upper respiratory infection		16.2[14]	12.5[14]				1.3	2.1
Miscellaneous								
Accidental injury	0 – 4.2	5.1	4.2		6	≥ 2		
Allergic reaction	0 – 2.8	2.3	1	Rare reports	Rare reports	< 1	< 1	Rare reports
Chest pain	≥ 2			0.5 – 1		≥ 2	2.6 – 4	
Infection	2.8 – 10.3				11	≥ 2		
Influenza symptoms	0 – 3.2	5.1	7.1		5	2.3	2.4	
Rash/pruritus	1.1 – 3.9	2.3[14]	1.6[14]	0.8 – 1.3		≥ 2	2.1 – 4	0.5 – 0.6
Urinary tract infection	≥ 2	1.6	2.7			2.3		
Visual disturbance	≤ 2			0.9 – 1.2		1.6		

Abbreviations: ER = extended-release dosage form; IR = immediate-release dosage form.
* Frequency data obtained from product package inserts and not from direct comparisons between drugs or dosage forms.

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Musculoskeletal Effects

Myalgia is the most common musculoskeletal effect (1.2 – 8.9%) of the statins and is also the most benign myotoxic effect.[2-8, 15-17] Myopathy and rhabdomyolysis are the principle serious adverse effects of the statins and have been reported with all the available statins.[2-8, 18, 19] Myopathy can progress to rhabdomyolysis, renal failure, and death in severe cases.[18] The reported prevalence of myopathy ranges from less than 0.1% to 3% during statin monotherapy.[9, 20, 21] Rhabdomyolysis is less common, with about 1 case reported with any lipid-lowering agent for every 100,000 treatment-years.[22] Approximately 55 – 58% of cases were associated with concomitant medications affecting statin metabolism, such as fibrates or cyclosporine.[17] The incidence of fatal rhabdomyolysis has been estimated to be approximately 0.15 deaths per 1 million prescriptions.[17] In a case series (n = 44), 43% of patients were able to tolerate continued therapy with either the same statin or another statin after resolution of myopathy symptoms.[23]

Risk with Individual Statins. There is no indication that one agent is safer than another in this regard.[2-8, 24] The available evidence suggests that risk is similar with all the available agents except rosuvastatin, which may be more likely to cause myopathy or rhabdomyolysis. This is extremely controversial. Several groups have attempted to identify the risk of myopathy or rhabdomyolysis for the individual statins, including two managed care organizations,[25, 26] the Canadian Adverse Drug Reaction Monitoring program,[27] staff members from the FDA,[28-30] two drug manufacturers,[31, 32] physicians,[12, 33] a consumer watchdog group,[34, 35] and the United Kingdom (UK) Medicines Control Agency.[15] These reports analyzed data from large pools of patients and reported rates in different ways and did not evaluate dose-equivalency. These analyses are summarized in Table 2. Because the denominators were different in each analysis, the rates may not be directly compared although postmarketing data are available for each agent.

In their retrospective analysis, Alsheikh-Ali et al[33] reported that risk of rhabdomyolysis was significantly greater with rosuvastatin than atorvastatin, pravastatin, or simvastatin, based on both reports made during the first year of marketing for each drug and reports made for all agents during rosuvastatin's first year of marketing. This analysis did not include fluvastatin or lovastatin.[33] Conversely, Cziraky et al[26] found no significant difference between the available agents in risk of myopathy requiring hospitalization. Although myopathy was not specifically evaluated, another retrospective analysis found that muscle symptoms (ie, heaviness, stiffness, cramps, weakness) were significantly more common with atorvastatin or simvastatin than pravastatin, and significantly less common with fluvastatin than pravastatin.[32] However, another retrospective analysis suggests that rosuvastatin or simvastatin may be more likely to cause rhabdomyolysis than the other statins, based on a huge disparity between the agents in number of reports.[12] None of the other analyses made any statistical comparisons between the individual agents. None of the analyses evaluated the possible existence of a dose-response relationship.[12, 15, 25, 27-31, 33-35]

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Table 2. Summary of Reports Evaluating the Risk of Statin-Induced Rhabdomyolysis

Study / Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	All Statins	Grade *
Prescriptions Solutions, 1999:[25] Frequency (number) of cases, based on retrospective review of ICD9 codes in a managed care organization database, from 7/1/99 – 12/1/99									4
Total cases	0.411% (123/29,916)	0.332% (41/12,340)	0.306% (98/31,941)	0.247% (2/809)	0.225% (120/53,169)	No data (not yet marketed)	0.189% (10/5,279)	0.295% (394/133,454)	
Statin monotherapy	0.427% (122/28,516)	0.223% (27/12,096)	0.307% (96/21,218)	0.25% (2/798)	0.255% (116/51,475)		0.195% (10/5,122)	0.288% (373/129,225)	
Statin plus gemfibrozil	0.071% (1/1,400)	5.737% (14/244)	0.276% (2/723)	0% (0/11)	0.236% (4/1,694)		0% (0/157)	0.496% (21/4,229)	
Managed Care Organization Claims Database (Cziraky et al), 2006:[26] Frequency (number) of cases, based on retrospective review of ICD9 codes in a managed care organization database, from 7/1/2000 – 12/1/2004									3
Person-years of exposure to statin monotherapy	261,567	4,719	12,635	26,122	64,254	8,213	54,394	490,988	
Myopathy requiring hospitalization (ie, myoglobinuria, rhabdomyolysis, or unspecified muscle disorders)	64	5	2	6	22	2	19	120	
Incidence/10,000 person-years)	2.45 (95% CI 1.9 – 3.1)	10.59 (95% CI 3.4 – 24.7, p < 0.05 vs. others)	1.58 (95% CI 0.2 – 5.7)	2.3 (95% CI 0.8 – 4.5)	3.42 (95% CI 2.1 – 5.2)	2.44 (95% CI 0.3 – 8.8)	3.49 (95% CI 2.1 – 5.5)	- -	
Health Protection Board, 2002:[27] Number of reports, based on retrospective review of Canadian Adverse Reaction Monitoring Program from product launch through 8/24/01									4
Year of Canadian product launch	1997	1998	1994	1988	1990	No data (not yet marketed)	1990	- -	
Rhabdomyolysis	10	54	0	12	3		7	- -	
Myopathy	32	8	5	24	17		34	- -	
Increased CPK with myopathy	16	11	1	6	4		6	- -	
Increased CPK without myopathy	5	6	0	4	6		5	- -	
Total reports of any adverse event	231	121	43	182	123		170	- -	
United Kingdom Medicines Control Agency, 2002:[15] Frequency (number) of cases, based on retrospective review of UK adverse event monitoring from 1/1/1994 – 1/1/2002									3
Total prescriptions dispensed	12,704,854	2,541,792	2,830,006	NR	6,016,920	No data (not yet marketed)	23,836,747	- -	
Rhabdomyolysis	0.0001% (13/12,704,854)	0.0004% (12/2,541,792)	0.00007% (2/2,830,006)	NR	0.00005% (3/6,016,920)		0.0002% (38/23,836,747)	- -	
Any musculoskeletal adverse event	0.003% (438/12,704,854)	0.01% (258/2,541,792)	0.005% (129/2,830,006)	NR	0.003% (177/6,016,920)		0.004% (875/23,836,747)	- -	
FDA Staff Member, 2002:[28] Number of reported cases, based on retrospective review of AERS from time of US product launch through 6/26/2001									3
Year of product launch	1996	1997	1993	1987	1991	No data (not yet marketed)	1991	- -	
Total number of prescriptions dispensed†	140,360,000	9,815,000	37,364,000	99,197,000	81,364,000		116,145,000	484,273,000	
Fatal rhabdomyolysis	6	31	0	19	3		14	73	
Rate‡ (cases/1 million prescriptions)	0.04	3.16	0	0.19	0.04		0.12	0.15	

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; CI = confidence interval; CPK = creatine phosphokinase.
Note: Gray shading in the evidence table indicates analyses added since the October 2003 review.
* Grade of Evidence. Refer to Appendix A for definitions.
† Prescriptions dispensed in US from time of product launch through end of study period, per data from National Prescription Audit Plus (Chang, Staffa) or IMS Health (Alsheikh-Ali).
‡ Reporting rate = number of cases divided by the number of prescriptions dispensed.
§ Two cases were counted twice (1 statin without fibrate death and 1 statin/fibrate death) because patients were receiving 2 statins concurrently. One patient received cerivastatin and simvastatin, while the other patient received pravastatin, simvastatin, and a fibrate.
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Study / Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	All Statins	Grade *
FDA Staff Member, 2004:[29] Number of reported cases, based on retrospective review of AERS from time of US product launch through 7/31/2001									3
Year of product launch	1996	1997	1993	1987	1991	No data (not yet marketed)	1991	- -	
Total number of prescriptions dispensed†									
Statin monotherapy	147,610,000	11,038,000	37,791,000	97,336,000	82,000,000		118,986,000	494,761,000	
Statin plus gemfibrozil	1,198,000	22,000	316,000	2,109,000	1,422,000		962,000	6,029,000	
Rhabdomyolysis									
Statin monotherapy	45	200	1	120	17		99	482	
Rate‡ (cases/million prescriptions)	0.3	18.1	0	1.2	0.2		0.8	1	
Statin plus gemfibrozil	6	279	0	60	2		37	384	
Rate‡ (cases/million prescriptions)	5	12486.6	0	28.4	1.4		38.5	63.6	
Fatal rhabdomyolysis									
Statin monotherapy	6	0	22	18	3		8	57	
Statin plus gemfibrozil	0	16	0	1	0		6	23	
FDA Staff Member, 2004:[30] Number of reports, based on retrospective review of ICD9 codes in 11 managed care health organization databases from 1/1/1998 – 6/30/2001									3
Person-years of exposure						No data (not yet marketed)			
Statin monotherapy	129,367	7,486	3,292	775	33,149		40,940	215,009 Minus Cerivastatin: 207,523	
Statin plus fibrate	2,664	89	25	10	543		552	3,883 Minus Cerivastatin: 3,794	
Rhabdomyolysis requiring hospitalization	8	10 (p = 0.002 vs. others)	0	0	0		3	21	
Statins monotherapy (percent of cases associated with specific agent)	7 (87.5%)	4 (40%)	0	0	0		2 (66.7%)	13 (61.9%) Minus Cerivastatin: 9	
Incidence per 10,000 person-years	0.54 (95% CI 0.22 – 1.12)	5.34 (95% CI 1.46 – 13.68)	- -	- -	- -		0.49 (95% CI 0.06 – 1.76)	0.60 Minus Cerivastatin: 0.43	
Statin plus fibrate (percent of cases associated with specific agent)	1 (12.5%)	6 (60%)	0	0	0		1 (33.3%)	8 (38.1%) Minus Cerivastatin: 2	
Incidence per 10,000 person-years	22.45 (95% CI 0.57 – 125)	1035 (95% CI 389 – 2117)	- -	- -	- -		18.73 (95% CI 0.47 – 104)	20.6 Minus Cerivastatin: 5.27	

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; CI = confidence interval; CPK = creatine phosphokinase.
Note: Gray shading in the evidence table indicates analyses added since the October 2003 review.
* Grade of Evidence. Refer to Appendix A for definitions.
† Prescriptions dispensed in US from time of product launch through end of study period, per data from National Prescription Audit Plus (Chang, Staffa) or IMS Health (Alsheikh-Ali).
‡ Reporting rate = number of cases divided by the number of prescriptions dispensed.
§ Two cases were counted twice (1 statin without fibrate death and 1 statin/fibrate death) because patients were receiving 2 statins concurrently. One patient received cerivastatin and simvastatin, while the other patient received pravastatin, simvastatin, and a fibrate.
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Table 2. Summary of Reports Evaluating the Risk of Statin-Induced Rhabdomyolysis (continued)

Study / Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	All Statins	Grade *
Alsheikh-Ali et al, 2005:[33] Number of reports, based on retrospective review of domestic reports received by AERS from 10/1/2003 – 9/30/2004 (first year of rosuvastatin marketing), and during first year of US marketing for each agent.									3
Year of product launch	1996	1997	1993	1987	1991	2003	1991	- -	
Total number of prescriptions dispensed†			Not included in analysis	Not included in analysis				Unable to calculate	
First year of marketing for each agent	Not reported	Not reported			Not reported	Not reported	Not reported		
Concurrent with first year of rosuvastatin marketing	72,900,000	No data (not marketed)			15,000,000	5,200,000	29,800,000		
Combined endpoint (rhabdomyolysis, proteinuria, nephropathy, or renal failure) (cases/1 million prescriptions)									
First year of marketing for each agent (estimated from figure)	2.4	76.7			2.8	27.6 (NS vs. Simvastatin, p < 0.05 vs. all others)	13.4		
Concurrent with first year of rosuvastatin marketing	4.3	No data			3.5	27.9 (p < 0.001 vs. others)	12.8		
Mean daily dose at time of event	21.8±1.4 mg				18.8±2.0 mg	16.7±1.2 mg	53.1±2.8 mg		
Mean duration of statin therapy before event	369±46 days				745±229 days	70±8 days (p < 0.05 vs. others)	731±68 days		
Mean number of concomitant medications	5.7±0.4				6.2±0.8	4.2±0.3 (p < 0.05 vs. Pravastatin)	5.0±0.4		
Patients requiring hospitalization	66%				83%	72%	76%		
Patients not needing hospitalization	24%				2%	26% (p < 0.05 vs. Pravastatin)	18%		
Deaths	10%				15%	2% (p < 0.05 vs. Atorvasta-tin, Pravastatin)	6%		
Rhabdomyolysis (cases/1 million prescriptions, estimated from figure)									
First year of marketing for each agent	1.7	77.8			0.6	16.7 (p < 0.05 vs. others)	0		
Concurrent with first year of rosuvastatin marketing	2.3	No data			1.7	16.2 (p < 0.05 vs. others)	11.5		
Muscle events without rhabdomyolysis (ie, myalgia, myopathy, elevated CPK) (cases/1 million prescriptions, estimated)									
First year of marketing for each agent	25	46.25			38.75	86.25 (p < 0.05 vs. others)	41.25		
Concurrent with first year of rosuvastatin marketing	6	No data			12	89.1 (p < 0.05 vs. others)	10.5		

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; CI = confidence interval; CPK = creatine phosphokinase.

Note: Gray shading in the evidence table indicates analyses added since the October 2003 review.

* Grade of Evidence. Refer to Appendix A for definitions.

† Prescriptions dispensed in US from time of product launch through end of study period, per data from National Prescription Audit Plus (Chang, Staffa) or IMS Health (Alsheikh-Ali).

‡ Reporting rate = number of cases divided by the number of prescriptions dispensed.

§ Two cases were counted twice (1 statin without fibrate death and 1 statin/fibrate death) because patients were receiving 2 statins concurrently. One patient received cerivastatin and simvastatin, while the other patient received pravastatin, simvastatin, and a fibrate.

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Table 2. Summary of Reports Evaluating the Risk of Statin-Induced Rhabdomyolysis (continued)

Study / Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	All Statins	Grade *
Davidson et al, 2006:[12] Number of reports, based on retrospective review of domestic reports received by AERS from 1/1/1998 – 12/31/2000, and from 1/1/2002 to 12/31/2004.									3
Exposure (eg, total prescriptions dispensed or person-years of exposure)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	
Rhabdomyolysis (cases/1 million prescriptions)									
Rate prior to cerivastatin withdrawal, 1998 – 2000‡	0.59	72.88	0.28	2.2	0.58	No data (not yet marketed)	2.32	1.07	
Rate after cerivastatin withdrawal, 2002 – 2004‡	1.67	No data (not marketed)	3.44	2.76	1.63	13.54	8.71	3.56	
Myopathy (cases/1 million prescriptions)									
Rate prior to cerivastatin withdrawal, 1998 – 2000‡	0.26	5.98	0.73	0.48	0.36	No data (not yet marketed)	0.53	0.38	
Rate after cerivastatin withdrawal, 2002 – 2004‡	0.59	No data	0.43	0.6	0.5	2.23	1.31	0.74	
Myositis (cases/1 million prescriptions)									
Rate prior to cerivastatin withdrawal, 1998 – 2000‡	0.32	9.96	0.11	1.34	0.25	No data (not yet marketed)	0.72	0.43	
Rate after cerivastatin withdrawal, 2002 – 2004‡	0.27	No data	1.29	0.54	0.44	2.37	1.21	0.57	
Novartis Pharmaceuticals Corporation HealthCare Management, 2002:[31] Number of reported cases, based on retrospective review of foreign and domestic reports received by AERS from 11/1997 – 3/2000									3
Rhabdomyolysis (percent of statin-related cases associated with specific agent)	73 (12.1%)	192 (32%)	10 (1.7%)	40 (6.7%)	71 (11.8%)	No data (not yet marketed)	215 (35.8%)	601	
Fatal rhabdomyolysis	7	7	1	4	8		11	38	
Deaths, as percent of cases associated with the specific agent	9.6%	3.6%	10%	10%	11.3%		5.1%	- -	
Public Citizen (consumer advocacy group), 2002:[36] Number of reported cases, based on retrospective review of AERS from 10/1997 – 12/2000									4
Rhabdomyolysis (percent of statin-related cases associated with the specific agent)	86 (11.1%)	387 (50.1%)	10 (1.3%)	32 (4.1%)	70 (9.1%)	No data (not yet marketed)	187 (24.2%)	772	
Statins without fibrates (percent of cases associated with specific drug)	73 (84.9%)	187 (48.3%)	8 (80%)	30 (93.8%)	62 (88.6%)		164 (87.7%)	524 (67.9%)	
Statins with fibrates (percent of cases associated with the specific drug)	13 (15.1%)	200 (51.7%)	2 (20%)	2 (6.7%)	8 (11.4%)		23 (12.3%)	248 (32.1%)	
Fatal rhabdomyolysis (percent of statin-related cases associated with the specific agent)	13 (18.1%)	20 (27.8%)	1 (1.4%)	5 (6.9%)	9 (12.5%)		24 (33.3%)	72§	
Statins without fibrates (percent of cases associated with specific drug)	11 (84.6%)	10 (50%)	1 (100%)	5 (100%)	8 (88.9%)		19 (79.2%)	54 (75%)§	
Statins with fibrates (percent of cases associated with specific drug)	2 (15.4%)	10 (50%)	0 (0%)	0 (0%)	1 (11.1%)		5 (20.8%)	18 (25%)§	

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; CI = confidence interval; CPK = creatine phosphokinase.
Note: Gray shading in the evidence table indicates analyses added since the October 2003 review.
* Grade of Evidence. Refer to Appendix A for definitions.
† Prescriptions dispensed in US from time of product launch through end of study period, per data from National Prescription Audit Plus (Chang, Staffa) or IMS Health (Alsheikh-Ali).
‡ Reporting rate = number of cases divided by the number of prescriptions dispensed.
§ Two cases were counted twice (1 statin without fibrate death and 1 statin/fibrate death) because patients were receiving 2 statins concurrently. One patient received cerivastatin and simvastatin, while the other patient received pravastatin, simvastatin, and a fibrate.
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Table 2. Summary of Reports Evaluating the Risk of Statin-Induced Rhabdomyolysis (continued)

Study / Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin	All Statins	Grade *
Public Citizen Review, 2005:[35] Number of reported cases, based on retrospective review of AERS from 10/1/2003 – 9/30/2004									4
Total number of prescriptions dispensed (did not report source of prescription data)	66,600,000	No data (no longer marketed)	2,100,000	8,000,000	15,000,000	5,200,000	29,800,000	126,700,000 Minus Rosuvastatin: 121,500,000	
Rhabdomyolysis	87		2	16	9	68	139	321 Minus Rosuva-statin: 253	
Reporting rate (cases per 1 million prescriptions)	1.3		0.95	2.0	0.6	13.1	4.7	2.5 Minus Rosuva-statin: 2.1	

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; CI = confidence interval; CPK = creatine phosphokinase.
Note: Gray shading in the evidence table indicates analyses added since the October 2003 review.
* Grade of Evidence. Refer to Appendix A for definitions.
† Prescriptions dispensed in US from time of product launch through end of study period, per data from National Prescription Audit Plus (Chang, Staffa) or IMS Health (Alsheikh-Ali).
‡ Reporting rate = number of cases divided by the number of prescriptions dispensed.
§ Two cases were counted twice (1 statin without fibrate death and 1 statin/fibrate death) because patients were receiving 2 statins concurrently. One patient received cerivastatin and simvastatin, while the other patient received pravastatin, simvastatin, and a fibrate.
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In their meta-analysis, Silva et al[11] compared the risk of myalgia with all of the available agents except rosuvastatin (Appendix B, Evidence Table 1). Again, the results are difficult to interpret because the investigators performed many two-agent comparisons. The authors did not report whether comparative risk of myalgia with lovastatin was evaluated. Atorvastatin was more likely to cause myalgia than fluvastatin, pravastatin, or simvastatin. Risk with fluvastatin was similar to simvastatin, and might be less than pravastatin. Risk was lower with pravastatin than simvastatin.[11] These results do not allow for any consistent ranking of myalgia risk.

A public safety interest group, Public Citizen, unsuccessfully petitioned the FDA to remove rosuvastatin from the market based on reports of rhabdomyolysis and renal failure submitted to regulatory agencies in the US, Canada and the UK.[36-39] In the FDA's clinical review of rosuvastatin, the frequency of rhabdomyolysis was higher in clinical trials of rosuvastatin 80 mg than in trials of other statins. It was also higher than that reported in reviews of statin safety (0.5% for rosuvastatin compared to 0 – 0.2% for other statins).[40] Although all cases of rhabdomyolysis occurred with rosuvastatin doses of 80 mg, it is unclear that the risk is less at lower doses since the number of patients exposed to the 20 mg and 40 mg doses in clinical trials was less than one-third that of the 80 mg dose.[40] AstraZeneca has issued a letter to prescribers in the UK recommending a starting dose of 10 mg/day or less and a maximum dose of 40 mg/day.

Risk Factors. Numerous patient-specific factors may increase risk of myopathy including hypothyroidism, renal insufficiency, hepatic dysfunction, hypertriglyceridemia, metabolic muscle disorders (ie, carnitine palmityl transferase II deficiency, McArdle disease, myoadenylate deaminase deficiency), diabetes, age greater than 80 years, small body frame, frailty, alcohol consumption, heavy exercise, trauma, or surgery associated with severe metabolic demands.[41, 42] Although it is difficult to compare the separate analyses and to evaluate the impact of patient-specific factors, the risks appear similar for the currently marketed agents.

Relationship To Statin Dose. Myopathy and rhabdomyolysis appear to be dose-related adverse effects, although exact frequency data are not available for each individual agent and dose.[8, 18] Although the exact mechanism is unknown, one animal study suggests myopathy may be related to exposure of muscle tissue to high concentrations of statins.[43] The statins inhibit mevalonate formation within striated muscle, reducing the amount of cholesterol precursors available for cell functioning.[18] One human trial found that high-dose statins alter sterol metabolism within the cell, although the clinical effect of this is unknown.[44] Increased systemic exposure to statins may also increase risk.[22] By increasing exposure, concurrent use of drugs that inhibit statin metabolism or increase bioavailability may increase the risk of myopathy.[18]

There are data evaluating the dose-relationship for simvastatin-associated rhabdomyolysis. The product labeling for simvastatin was revised in 2003 to include statements that myopathy is a dose-related adverse effect.[8] No post-marketing data are available assessing the risk of myopathy, increased creatine phosphokinase (CPK), or rhabdomyolysis with each approved simvastatin dose. However, some frequency data are available from several published clinical trials and from the manufacturer.[45] Table 3 summarizes the results of clinical trials with simvastatin and other statins. These data are difficult to interpret since the trials lacked the statistical power to detect significant differences between the groups. Skeletal muscle toxicity

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was not the primary endpoint of the studies and screening methods for this side effect varied between the individual trials. In addition, percentages cannot be directly compared since denominators were different in each trial.

The exact incidence or risk of rhabdomyolysis with different statin doses cannot be quantified. No information was found during a search of Medline, the Cochrane Database, several evidence-based medicine sites (Bandolier, Oxford CATbank, TRIP Database), and the Internet, or from consultations with drug manufacturers. A letter from Merck states that the risk of rhabdomyolysis is dose-related but does not provide exact incidence data.[45]

Table 3. Dose-Relationship Of Musculoskeletal Adverse Effects In Statin Trials

	Frequency (n)				
Reference / Statin Regimen	**Increase in CPK from Baseline**	**Increase in CPK More than 10x ULN**	**Myalgia**	**Myopathy***	**Rhabdo-myolysis**
TNT Study, 2005[46]	NR	NR		NR	
Atorvastatin 10 mg			4.7%		0.06%
Atorvastatin 80 mg			4.8%		0.04%
Magnani et al, 2001[47]		NR	NR	NR	NR
Atorvastatin 10 mg	2.6% (1/39)				
Atorvastatin 20 mg	2.6% (1/39)				
Pravastatin 20 mg	2.6% (1/39)				
Pravastatin 40 mg	2.6% (1/39)				
PROVE IT-TIMI, 2004[48]	NR	NR		NR	
Atorvastatin 80 mg			3.3%		0%
Pravastatin 40 mg			2.7%		0%
MERCURY II Trial, 2006[49]	NR		NR		
Atorvastatin 10 mg		0.3%		0%	0%
Atorvastatin 20 mg		0 – 0.5%		0%	0%
Rosuvastatin 10 mg		0%		0%	0%
Rosuvastatin 20 mg		0.1 – 0.3%		0 – 0.1%	0%
Simvastatin 20 mg		0%		0%	0%
Simvastatin 40 mg		0%		0%	0%
ARIES Study, 2006[50]	NR				
Atorvastatin 10 mg		0%	2.6% (5/195)	0%	0%
Atorvastatin 20 mg		0%	1% (2/192)	0%	0%
Rosuvastatin 10 mg		0%	2.6% (5/195)	0%	0%
Rosuvastatin 20 mg		0%	3.6% (7/196)	0%	0%
Olsson et al, 2001[51]	NR	NR		NR	NR
Atorvastatin 10 mg			6.7% (1/15)		
Atorvastatin 80 mg			7.7% (1/13)		
Rosuvastatin 1 mg			0% (0/15)		
Rosuvastatin 2.5 mg			0% (0/15)		
Rosuvastatin 5 mg			5.6% (1/18)		
Rosuvastatin 10 mg			0% (0/17)		
Rosuvastatin 20 mg			5.9% (1/17)		
Rosuvastatin 40 mg			2.9% (1/34)		
Rosuvastatin 80 mg			3.2% (1/31)		

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Table 3. Dose-Relationship Of Musculoskeletal Adverse Effects In Statin Trials (continued)

Reference / Statin Regimen	Frequency (n)				
	Increase in CPK from Baseline	**Increase in CPK More than 10x ULN**	**Myalgia**	**Myopathy***	**Rhabdo-myolysis**
Schneck et al, 2003[52]		NR		NR	NR
Atorvastatin 10 mg	0% (1/43)		7% (3/43)		
Atorvastatin 20 mg	2.6% (1/39)		0% (0/39)		
Atorvastatin 40 mg	4.8% (0/39)		2.4% (1/42)		
Atorvastatin 80 mg	4.9% (3/41)		2.4% (1/41)		
Rosuvastatin 5 mg	0% (0/38)		0% (0/38)		
Rosuvastatin 10 mg	0% (0/45)		2.2% (1/45)		
Rosuvastatin 20 mg	0% (0/39)		0% (0/39)		
Rosuvastatin 40 mg	4.4% (2/45)		4.4% (2/45)		
Rosuvastatin 80 mg	0% (0/42)		2.4% (1/42)		
PRIMO Study, 2005[32]	NR	NR		NR	NR
Atorvastatin 40 – 80 mg			14.9% (274/1844)		
Fluvastatin 80 mg			5.1% (159/3121)		
Pravastatin 40 mg			10.9% (208/1901, $p < 0.05$ vs. others)		
Simvastatin 40 – 80 mg			18.2% (187/1027)		
Stein et al, 2003[53]					
Atorvastatin 80 mg	NR	0% (0/187)	3% (5/187)	0% (0/187)	NR
Rosuvastatin 80 mg	NR	0% (0/435)	4% (16/435)	0% (0/435)	NR
Karalis et al, 2002[54]	More than 3x ULN	NR	NR	NR	NR
Atorvastatin 10 mg	0% (0/571)				
Atorvastatin 80 mg	0% (0/196)				
Simvastatin 20 mg	0% (0/585)				
Simvastatin 80 mg	1.1% (2/181)				
Recto et al, 2000[55, 56]	NR			NR	NR
Atorvastatin 10 mg		0% (0/127)	4.7% (6/127)		
Atorvastatin 20 mg		0% (0/128)	0% (0/129)		
Simvastatin 20 mg		0% (0/127)	1.6% (2/128)		
Simvastatin 40 mg		0% (0/126)	2.4% (3/127)		
CHESS Investigators, 2003[57]	More than 5x ULN				NR
Atorvastatin 80 mg	0.2% (1/464)	0% (0/464)	NR	0% (0/464)	
Simvastatin 80 mg	0.2% (1/453)	0.2% (1/453)	NR	0% (0/453)	
Expanded Clinical Evaluation of Lovastatin (EXCEL) Study, 1991[58-60]					NR
Lovastatin 20 mg once daily	28.8% (473/1642)	0.2% (3/1642)	8.3% (137/1642)	0% (0/1642)	
Lovastatin 40 mg once daily	29.8% (490/1645)	0.2% (3/1645)	6.7% (111/1645)	0.1% (1/1645)	
Lovastatin 20 mg BID	31.9% (525/1646)	0.2% (3/1646)	7.1% (116/1646)	0% (0/1646)	
Lovastatin 40 mg BID	34.7% (572/1649)	0.5% (8/1649)	9.3% (153/1649)	0.2% (4/1649)	
Crouse et al, 2002[61]	NR	NR		NR	NR
Lovastatin 10 mg ER			0% (0/33)		
Lovastatin 20 mg ER			5.9% (2/34)		
Lovastatin 40 mg ER			3% (1/33)		
Lovastatin 60 mg ER			2.8% (1/35)		

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Table 3. Dose-Relationship Of Musculoskeletal Adverse Effects In Statin Trials (continued)

Reference / Statin Regimen	Frequency (n)				
	Increase in CPK from Baseline	**Increase in CPK More than 10x ULN**	**Myalgia**	**Myopathy***	**Rhabdo-myolysis**
FDA review of phase II/III clinical trials, 2003[37, 62]			NR		
	More than 5x ULN				
Rosuvastatin 5 mg	1.1% (14/1317)	0.4% (5/1317)		0.2% (3/1317)	0% (0/1317)
Rosuvastatin 10 mg	0.9% (69/7727)	0.2% (17/7727)		0.1% (9/7727)	0.01% (1/7727)
Rosuvastatin 20 mg	0.5% (19/3883)	0.2% (7/3883)		0.1% (7/3883)	0% (0/3883)
Rosuvastatin 40 mg	1.1% (39/3700)	0.4% (15/3700)		0.2% (6/3700)	0% (0/3700)
Rosuvastatin 80 mg	3.5% (55/1574)	1.9% (30/1574)		1% (16/1574)	0.4% (7/1574)
Davidson et al, 2002[63]	NR	NR		NR	NR
Rosuvastatin 5 mg			0.8% (1/128)		
Rosuvastatin 10 mg			0.8% (1/129)		
Olsson et al, 2002[64]	NR			NR	NR
Rosuvastatin 5 – 80 mg (mean = 9 mg)		0.7% (1/136)	6.6% (9/136)		
Rosuvastatin 10 – 80 mg (mean = 13 mg)		0% (0/132)	3.8% (5/132)		
Brown et al, 2002[65]		NR		NR	NR
Rosuvastatin 5 – 80 mg (mean = 10 mg)	2.4% (3/123)		3.3% (4/123)		
Rosuvastatin 10 – 80 mg (mean = 14 mg)	3.5% (4/115)		4.3% (5/115)		
Stein et al, 1990[66]	50 U/L or more	NR	NR	NR	NR
Simvastatin 20 mg	4.8% (4/84)				
Simvastatin 40 mg	8.6% (7/82)				
A to Z trial, Phase Z, 2004[67]	NR		NR		
Simvastatin 20 mg		0%		0.04% (1/2,232)	0%
Simvastatin 80 mg		0.04% (1/2,265)		0.26% (6/2,265)	0.13% (3/2,265)
Stein et al, 1998[68]	NR	NR	NR		NR
Simvastatin 40 mg				0% (0/207)	
Simvastatin 80 mg				0.6% (2/314)	
Pietro et al, 1989[69]	50 U/L or more	NR	NR	NR	NR
Simvastatin 20 mg	2.5% (2/82)				
Simvastatin 40 mg	7.5% (6/80)				
Ose et al, 1998[45, 70]	NR	NR		NR	NR
Simvastatin 40 mg			3.5% (15/436)		
Simvastatin 80 mg			4.8% (32/669)		

Abbreviations: CPK = creatine phosphokinase; n = number of patients in group; NR = not reported: ULN = upper limit of normal.
Note: Gray shading in the table indicates trials added since the October 2003 review.
* Defined as increase in CPK above 10x ULN in conjunction with muscle symptoms

Hepatic Effects

No clinical trials have evaluated the comparative risk of hepatotoxicity with the statins. The available evidence suggests that risk is similar with the available agents. Increased hepatic transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) have occurred with all the available statins, usually within the first 3 months of therapy. The frequency ranges from 0.5 – 2% and increases with the statin dose.[2-8, 24, 71] One study reported a higher prevalence of elevation of ALT greater than 3 times the upper limit of normal (ULN) with atorvastatin (2.8%) than simvastatin (0.4%, p=0.007).[57] Acute liver failure and hepatotoxicity are rare; serious liver injury occurs with an overall frequency of 0.2 per 100,000 persons exposed, which is less than the risk in the general population.[72]

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Two meta-analyses have evaluated the risk of hepatic adverse effects (Appendix B, Evidence Table 1).[11, 73] Their results are difficult to interpret because the investigators performed many two-agent comparisons, rather than comparing the entire group. De Denus et al[73] reviewed 13 controlled trials and found that the risk of increased liver function tests (LFTs) with pravastatin or simvastatin was similar to placebo. Compared with placebo, risk was significantly higher with fluvastatin (OR 3.4, 95% CI 1.1 – 11.6, p = 0.04), and there was a trend towards higher risk with lovastatin (OR 1.78, 95% CI 0.8 – 3.9, p = 0.14).[73] In their meta-analysis, Silva et al[11] compared the risk of increased LFTs with all the available agents except rosuvastatin. The authors did not report whether comparative risk of increased LFTs with lovastatin was evaluated. Atorvastatin was more likely to cause increased LFTs than fluvastatin, pravastatin, or simvastatin. Risk with fluvastatin was less than simvastatin or pravastatin. Risk was lower with simvastatin than pravastatin.[11]

Several retrospective analyses have attempted to identify the risk of hepatic adverse events for the available statins including physicians reviewing the FDA adverse event database,[12, 33] the World Health Organization adverse event database,[74] and managed care organization databases.[26, 75] These reports analyzed data from large pools of patients, reported rates in different ways, and did not evaluate dose-equivalency (Appendix B, Evidence Table 1). Because the denominators differed in each analysis, the rates may not be directly compared.

In their retrospective analysis, Alsheikh-Ali[33] reported that risk of hepatic adverse effects was significantly greater with rosuvastatin than atorvastatin, pravastatin, or simvastatin based on reports made for all agents during rosuvastatin's first year of marketing. Based on reports made during the first year of marketing for each drug, hepatic adverse effects were significantly more common with rosuvastatin than atorvastatin or pravastatin. This analysis did not include fluvastatin or lovastatin.[33] Cziraky et al[26] found no significant difference between the available agents in risk of liver events requiring hospitalization. Perger et al[74] reported that risk of fatal liver failure was similar with atorvastatin, fluvastatin, lovastatin, pravastatin, or simvastatin; rosuvastatin was not included in this analysis.[74] Although no statistical comparisons were made, one retrospective analysis suggests that rosuvastatin or simvastatin may be more likely to cause liver failure or hepatitis than the other statins, based on a huge disparity between the agents in number of spontaneous reports to the FDA.[12] The other retrospective analysis did not make any statistical comparisons between the available statins. None of the analyses evaluated the possible existence of a dose-response relationship.[12, 26, 33, 74, 75]

The FDA and the drug manufacturers recommend reducing the dose or discontinuing therapy in patients with persistent elevations more than 3 times ULN.[71] The product labeling for each of the statins recommends monitoring liver function tests at baseline, 6 – 12 weeks after initiating therapy or increasing the dose, and every 6 months thereafter.[2-8] In a 2006 consensus statement, the Liver Expert Panel of the National Lipid Association's Safety Task Force recommended against routinely monitoring liver function tests in asymptomatic patients.[76] Table 4 summarizes the relationship between dose and frequency of increased ALT.

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Table 4. Relationship Between Statin Dose and Frequency of Transaminases Persisting Above 3 times the Upper Limit of Normal*[2-8, 73, 77, 78]

Dose	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
0 mg (Placebo)	NR	0.28%	0.1%	1.3%	NR	0.6%
10 mg	0.2%	NR	NR	NR	0.1%	NR
20 mg	0.2%	0.2%	0.1 – 0.7%	NR	0.1%	0.7%
40 mg	0.6%	1.5 – 1.8%	0.4 – 0.9%	1.4%	0.1 – 4%	0.9%
80 mg	2.3%	1.9 – 4.9%	1.5%	NR	1.4%	2.1%
All doses combined	0.7%	1.1%	1.9%	NR	NR	1%

Abbreviations: NR = not reported.

* Frequency extracted from package inserts, FDA rosuvastatin briefing document, and the de Denus meta-analysis, rather than from direct comparisons in head-to-head clinical trials.

How Does The Risk of Renal Side Effects Compare For The Various Statins?

No trials have evaluated the comparative risk of renal toxicity with the statins. Renal effects are extremely rare. The available evidence suggests that risk is similar with the available agents, although the risk appeared higher with rosuvastatin in some retrospective analyses. Several retrospective analyses have attempted to identify the risk of renal toxicity for the available statins including physicians reviewing the FDA adverse event database,[12, 33] and a managed care organization database[26] and a consumer watchdog group reviewing the FDA adverse event database.[38] These reports analyzed data from large pools of patients, reported rates in different ways, and did not evaluate dose-equivalency (Appendix B, Evidence Table 1). Because the denominators differed in each analysis, the rates may not be directly compared.

In their retrospective analysis, Alsheikh-Ali et al[33] reported that risk of both proteinuria and renal failure were significantly greater with rosuvastatin than atorvastatin, pravastatin, or simvastatin based on reports made for all agents during rosuvastatin's first year of marketing. Based on reports made during the first year of marketing for each drug, proteinuria was significantly more common with rosuvastatin than atorvastatin and was numerically more common with simvastatin than the other agents (no statistical comparison reported). Renal failure was significantly more common with rosuvastatin than atorvastatin or pravastatin in the same analysis. This analysis did not include fluvastatin or lovastatin.[33] Conversely, Cziraky et al[26] found that risk of renal events requiring hospitalization was significantly higher with simvastatin than any other agent, but was similar for the other available agents. The other two analyses did not make any statistical comparisons between the available statins.[12, 38] However, both analyses suggest that rosuvastatin may be more likely to cause renal failure or renal dysfunction than the other statins, based on a huge disparity between the agents in number of spontaneous reports to the FDA.[12, 38]

Rosuvastatin was associated with dose-related persistent proteinuria and microscopic hematuria during clinical trials.[3, 37] In the FDA's clinical review, the prevalence of proteinuria and hematuria was higher in subjects given rosuvastatin 40 mg or 80 mg, compared to those given lower rosuvastatin doses, placebo, or up to 80 mg of atorvastatin.[40] The prevalence of increased proteinuria (at least 1 grade from baseline) was 12.6% with rosuvastatin 5 mg/day,

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9.7% with rosuvastatin 10 mg/day, 13.8% with rosuvastatin 20 mg/day, 25.2% with rosuvastatin 40 mg/day, and 31.9% with rosuvastatin 80 mg/day. These effects are transient and are not associated with significant renal dysfunction at labeled rosuvastatin doses. However, there are data suggesting that renal dysfunction may occur in a subset of patients with proteinuria and hematuria. In rosuvastatin patients with dipstick-confirmed proteinuria/hematuria, serum creatinine increased at least 30% from baseline in 14% of patients given rosuvastatin 5 mg/day, 16% of those given 10 mg/day, 24% of those given 20 mg/day, and 33% of those given rosuvastatin 40 mg/day, and 41% of those given 80 mg/day.[3, 37] One controlled trial found no significant change in estimated glomerular filtration rate (GFR) with rosuvastatin 10 mg/day for 20 weeks in 91 patients with chronic kidney disease.[79] A post-hoc analysis of the rosuvastatin clinical trial program found that estimated GFR increased slightly with rosuvastatin 5 – 40 mg/day (0.8±6.9 mL/min, 95% CI +0.1 to +1.5) and decreased slightly with placebo (-1.5±6.1 mL/min, 95% CI -0.5 to -2.5, $p < 0.001$ vs. rosuvastatin) after up to 8 weeks.[80] Renal dysfunction (1 case) and renal failure (2 cases) have been reported with rosuvastatin 80 mg/day in conjunction with proteinuria and hematuria; none of the cases resulted from rhabdomyolysis. Proposed mechanisms for the renal failure include tubular inflammation and necrosis, based on renal biopsies from the reported cases.[3, 37]

No additional monitoring is recommended for detecting these adverse events during rosuvastatin therapy. However, the labeled dosage range of rosuvastatin should not be exceeded. In addition, the manufacturer recommends dosage reduction if unexplained proteinuria occurs during therapy with rosuvastatin 40 mg/day.[3, 37] In a pooled analysis of 49 atorvastatin trials,[81] treatment-related hematuria occurred in 0.02% of patients treated with atorvastatin 80 mg/day and in no patients given atorvastatin 10 mg/day. Albuminuria was not reported with atorvastatin 10 mg/day or 80 mg/day.[81] These events have not usually been associated with the other available statins and are not reported in the product labeling.[2-8, 37] Table 5 summarizes the frequency of renal adverse effects noted in the FDA Clinical Review of the rosuvastatin clinical trials program.[78]

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Table 5. Relationship Between Statin Dose and Frequency of Renal Adverse Effects*[78, 82]

Drug / Dose	Proteinuria (at least Grade 2) or Hematuria (at least Grade 1)			Effects on Creatinine Clearance	
	Proteinuria Only	Hematuria Only	Proteinuria and Hematuria	Patients with Serum Creatinine Increased more than 30 % from Baseline	Creatinine Clearance, Mean Change from Baseline
Dietary Run-In	1%	3%	0.1%	NR	NR
Placebo	3%	5%	0%	NR	+0.42%
Atorvastatin				NR	
10 mg	2%	4%	0.6%		-2.04%
20 mg	2%	3%	0.3%		-2.04%
40 mg	0.4%	2%	0.4%		-2.06%
80 mg	0.5%	2%	0%		-4,12%
Pravastatin				NR	
10 mg	NR	NR	NR		-2.08%
20 mg	1%	7%	0.5%		-2.06%
40 mg	0%	4%	0%		-1.02%
Rosuvastatin					
5 mg	1%	6%	0%	0.1%	-2.06%
10 mg	2%	7%	0.3%	0%	-2.04%
20 mg	2%	4%	0.3%	0%	-2.08%
40 mg	4%	10%	1.3%	0.2%	-2.13%
80 mg	12%	12%	6.1%	2.6%	NR
Simvastatin				NR	
10 mg	NR	NR	NR		-0.86%
20 mg	4%	5%	0.6%		-2.04%
40 mg	2%	5%	0.8%		-2.08%
80 mg	0.6%	8%	0.3%		-2.17%

Abbreviations: NR = not reported, unknown if endpoint was assessed.

* Data extracted from the FDA rosuvastatin briefing document[78] and a post-hoc analysis,[82] both of which reviewed data from head-to-head comparisons in rosuvastatin clinical trials, although no statistical comparisons were made between agents for these endpoints. The rosuvastatin clinical trials program submitted with the NDA did not include comparisons with fluvastatin or lovastatin.

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Appendix A: Grades of Scientific Evidence

Grade 1. Evidence from randomized, blinded, placebo-controlled, clinical trials in peer reviewed journals.
Grade 2. Non-randomized controlled trials.
Grade 3. Non-randomized historical cohort studies. Other studies with non-experimental designs (eg, population based studies, case-control studies).
Grade 4. Case reports, case series, abstracts of trials.
Grade 5. Consensus of experts where data are incomplete or inconsistent.

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Evidence Table 1. Publications Evaluating the Comparative Risk of Adverse Events

Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Silva et al, 2006[11] Meta-analysis of 18 experimental, parallel or crossover, randomized, double-blind, placebo-controlled trials[46, 51, 63, 67, 83-97]	71,108	Trials at least 6 weeks in duration; evaluating efficacy for primary or secondary prevention and reporting adverse event rates.	Statin, given at fixed or titrated dose (N = 36,062): • Atorvastatin (5 trials) • Fluvastatin (3 trials) • Lovastatin (1 trial) • Pravastatin (6 trials) • Rosuvastatin (2 trials) • Simvastatin (3 trials) Placebo (N = 35,046) Duration – 6 weeks – 6.1 years, for a total of 301,374 person-years of follow-up. Did not report doses used or the number of patients treated with each agent.	Adverse effects: More common with Statins than Placebo	*All Statins combined vs. Placebo:* Any adverse effect: • Statins: 2,.8%, 1017 events • Placebo: 2.3%, 811 events (p = 0.008) • OR 1.4, 95% CI 1.09 – 1.8, NNH = 197 Myopathy-related events: • Statins: 0.88%, 316 events • Placebo: 0.72%, 253 events (p < 0.001) CPK increased from baseline: • Statin: 0.22%, 81 events • Placebo: 0.18%, 64 events (p = 0.001) CPK greater than 10 times ULN or rhabdomyolysis: • Slightly lower risk with Placebo than Statins (absolute risk reduction 0.03%, NS) • NNH = 3,400 Rhabdomyolysis: • Statins: 0.027%, 10 events o Lovastatin: 1 events o Simvastatin: 9 events • Placebo: 0.014%, 5 events (absolute risk reduction 0.1%, NS) • NNH = 7,428 LFTs increased at least 3 times ULN: • Statin: 1.7%, 609 events • Placebo: 1.4%, 487 events (p = 0.002) *Results continued on next page*	1

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
Grade of Evidence. Refer to Appendix A for definitions.

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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Silva et al, 2006[11] Meta-analysis of 18 experimental, parallel or crossover, randomized, double-blind, placebo-controlled trials (see first page for study references)	71,108	Trials at least 6 weeks in duration; evaluating efficacy for primary or secondary prevention and reporting adverse event rates.	*See previous page*	Adverse effects: More common with Atorvastatin, followed by Fluvastatin, Pravastatin, or Simvastatin. Similar with Lovastatin and other statins. Similar with Fluvastatin and Simvastatin. Lower with Fluvastatin than Pravastatin. Similar with Pravastatin and Simvastatin.	*Statins vs. Each Other:* Atorvastatin vs. Fluvastatin • Any event: less common with Fluvastatin (OR 0.26, 95% CI 0.2 – 0.34, p < 0.001) • Myalgia: less common with Fluvastatin (OR 0.28, 95% CI 0.18 – 0.44, p < 0.001) • LFT increase: less common with Fluvastatin (OR 0.25, 95% CI 0.13 – 0.45, p < 0.001) Atorvastatin vs. Lovastatin: • Any event: similar with Lovastatin (OR not reported, NS) Atorvastatin vs. Pravastatin: • Any event: less common with Pravastatin (OR 0.51, 95% CI 0.42 – 0.6, p < 0.001) • Myalgia: less common with Pravastatin (OR 0.43, 95% CI 0.36 – 0.51, p < 0.001) • LFT increase: less common with Pravastatin (OR 0.57, 95% CI 0.47 – 0.7, p < 0.001) Atorvastatin vs. Simvastatin: • Any event: less common with Simvastatin (OR 0.57, 95% CI 0.32 – 1.0, p = 0.048) • Myalgia: less common with Simvastatin (OR 0.23, 95% CI 0.19 – 0.28, p < 0.001) • LFT increase: less common with Simvastatin (OR 0.7, 95% CI 0.57 – 0.86, p < 0.001) Fluvastatin vs. Lovastatin: • Any event: similar with Lovastatin (OR not reported, NS) *Results continued on next page*	1

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
Grade of Evidence. Refer to Appendix A for definitions.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Silva et al, 2006[11] Meta-analysis of 18 experimental, parallel or crossover, randomized, double-blind, placebo-controlled trials (see first page for study references)	71,108	Trials at least 6 weeks in duration; evaluating efficacy for primary or secondary prevention and reporting adverse event rates.	*See previous page*	Adverse effects: More common with Atorvastatin, followed by Fluvastatin, Pravastatin, or Simvastatin. Similar with Lovastatin and other statins. Similar with Fluvastatin and Simvastatin. Lower with Fluvastatin than Pravastatin. Similar with Pravastatin and Simvastatin.	*Continued from previous page* *Statins vs. Each Other:* Fluvastatin vs. Pravastatin: • Any event: less common with Fluvastatin (OR 0.54, 95% CI 0.42 – 0.69, p < 0.001) • Myalgia: may be less common with Fluvastatin (OR 0.64, 95% CI 0.41 – 1.02, p = 0.059) • LFT increase: less common with Fluvastatin (OR 0.43, 95% CI 0.23 – 0.79, p = 0.006) Fluvastatin vs. Simvastatin: • Any event: similar with Fluvastatin (OR 0.58, 95% CI 0.31 – 1.11, NS) • Myalgia: similar with Fluvastatin (OR 1.212, 95% CI 0.76 – 1.93, NS) • LFT increase: less common with Fluvastatin (OR 0.35, 95% CI 0.19 – 0.64, p = 0.001) Lovastatin vs. Pravastatin: • Any event: similar with Lovastatin (OR 1.19, 95% CI 1.03 – 1.37, NS) Lovastatin vs. Simvastatin: • Any event: similar with Lovastatin (OR not reported, NS) Pravastatin vs. Simvastatin: • Any event: similar with Pravastatin (OR 1.01, 95% CI 0.67 – 1.51, NS) • Myalgia: less common with Pravastatin (OR 0.53, 95% CI 0.44 – 0.65, p < 0.001) • LFTs increase: more common with Pravastatin (OR 1.23, 95% CI 1.03 – 1.46, p = 0.022)	1

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
Grade of Evidence. Refer to Appendix A for definitions.

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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Davidson et al, 2006[12] Observational, retrospective review of AERS	Did not report	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates : • Prior to cerivastatin withdrawal (1998 – 2000) • After cerivastatin withdrawal (2002 – 2004)	Atorvastatin, dose not reported (n = not reported) Cerivastatin, dose not reported (n = not reported) Fluvastatin, dose not reported (n = not reported) Lovastatin, dose not reported (n = not reported) Pravastatin, dose not reported (n = not reported) Rosuvastatin, dose not reported (n = not reported) Simvastatin, dose not reported (n = not reported) Duration – not applicable, retrospective analysis	*Prior to cerivastatin withdrawal, 1998 – 2000:* Adverse effects: More common with Cerivastatin, followed by Simvastatin, Atorvastatin, Lovastatin, Fluvastatin, and Pravastatin.	*Prior to cerivastatin withdrawal, 1998 – 2000:* All adverse events: • All statins: 38.15 cases/million prescriptions • Atorvastatin: 37.79 cases/million prescriptions • Cerivastatin: 222.4 cases/million prescriptions • Fluvastatin: 18.6 cases/million prescriptions • Lovastatin: 36.3 cases/million prescriptions • Pravastatin: 10.5 cases/million prescriptions • Simvastatin: 65.08 cases/million prescriptions Fatal adverse events • All statins: 0.83 cases/million prescriptions • Atorvastatin: 0.98 cases/million prescriptions • Cerivastatin: 9.96 cases/million prescriptions • Fluvastatin: 0.28 cases/million prescriptions • Lovastatin: 1.62 cases/million prescriptions • Pravastatin: 0.38 cases/million prescriptions • Simvastatin: 4.21 cases/million prescriptions Serious adverse events • All statins: 16.65 cases/million prescriptions • Atorvastatin: 20.69 cases/million prescriptions • Cerivastatin: 187.9 cases/million prescriptions • Fluvastatin: 7.76 cases/million prescriptions • Lovastatin: 18.25 cases/million prescriptions • Pravastatin: 9.59 cases/million prescriptions • Simvastatin: 17.48 cases/million prescriptions Note: no statistical comparisons made between the individual agents. *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Davidson et al, 2006[12] Observational, retrospective review of AERS	Did not report	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates : • Prior to cerivastatin withdrawal (1998 – 2000) • After cerivastatin withdrawal (2002 – 2004)	*See previous page*	*Prior to cerivastatin withdrawal, 1998 – 2000:* Adverse effects: More common with Cerivastatin, followed by Simvastatin, Atorvastatin, Lovastatin, Fluvastatin, and Pravastatin.	*Continued from previous page* *Prior to cerivastatin withdrawal, 1998 – 2000:* Rhabdomyolysis: • All statins: 1.07 cases/million prescriptions • Atorvastatin: 0.59 cases/million prescriptions • Cerivastatin: 72.88 cases/million prescriptions • Fluvastatin: 0.28 cases/million prescriptions • Lovastatin: 2.2 cases/million prescriptions • Pravastatin: 0.58 cases/million prescriptions • Simvastatin: 2.32 cases/million prescriptions Liver failure / hepatitis: • All statins: 0.69 cases/million prescriptions • Atorvastatin: 0.67 cases/million prescriptions • Cerivastatin: 7.12 cases/million prescriptions • Fluvastatin: 0.67 cases/million prescriptions • Lovastatin: 0.96 cases/million prescriptions • Pravastatin: 0.76 cases/million prescriptions • Simvastatin: 0.67 cases/million prescriptions Renal failure: • All statins: 0.30 cases/million prescriptions • Atorvastatin: 0.35 cases/million prescriptions • Cerivastatin: 4.84 cases/million prescriptions • Fluvastatin: 0.28 cases/million prescriptions • Lovastatin: 0.10 cases/million prescriptions • Pravastatin: 0.13 cases/million prescriptions • Simvastatin: 0.36 cases/million prescriptions Note: no statistical comparisons made between the individual agents. *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Davidson et al, 2006[12] Observational, retrospective review of AERS	Did not report	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates : • Prior to cerivastatin withdrawal (1998 – 2000) • After cerivastatin withdrawal (2002 – 2004)	*See previous page*	*After cerivastatin withdrawal, 2002 – 2004:* Adverse effects: More common with Rosuvastatin, followed by Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, and Lovastatin.	*Continued from previous page* *After cerivastatin withdrawal, 2002 – 2004:* All adverse events: • All statins: 32.32 cases/million prescriptions • Atorvastatin: 18.36 cases/million prescriptions • Fluvastatin: 32.43 cases/million prescriptions • Lovastatin: 16.66 cases/million prescriptions • Pravastatin: 48.46 cases/million prescriptions • Rosuvastatin: 340.5 cases/million prescriptions • Simvastatin: 36.35 cases/million prescriptions Fatal adverse events • All statins: 1.17 cases/million prescriptions • Atorvastatin: 0.85 cases/million prescriptions • Fluvastatin: 1.78 cases/million prescriptions • Lovastatin: 1.14 cases/million prescriptions • Pravastatin: 1.13 cases/million prescriptions • Rosuvastatin: 4.21 cases/million prescriptions • Simvastatin: 1.68 cases/million prescriptions Serious adverse events • All statins: 28.25 cases/million prescriptions • Atorvastatin: 17.72 cases/million prescriptions • Fluvastatin: 31.76 cases/million prescriptions • Lovastatin: 15.04 cases/million prescriptions • Pravastatin: 20.99 cases/million prescriptions • Rosuvastatin: 336.7 cases/million prescriptions • Simvastatin: 35.01 cases/million prescriptions Note: no statistical comparisons made between the individual agents. *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Davidson et al, 2006[12] Observational, retrospective review of AERS	Did not report	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates : • Prior to cerivastatin withdrawal (1998 – 2000) • After cerivastatin withdrawal (2002 – 2004)	*See previous page*	*After cerivastatin withdrawal, 2002 – 2004:* Adverse effects: More common with Rosuvastatin, followed by Pravastatin, Simvastatin, Fluvastatin, Atorvastatin, and Lovastatin.	*Continued from previous page* *After cerivastatin withdrawal, 2002 – 2004:* Rhabdomyolysis: • All statins: 3.56 cases/million prescriptions • Atorvastatin: 1.67 cases/million prescriptions • Fluvastatin: 3.44 cases/million prescriptions • Lovastatin: 2.76 cases/million prescriptions • Pravastatin: 1.63 cases/million prescriptions • Rosuvastatin: 13.54 cases/million prescriptions • Simvastatin: 8.71 cases/million prescriptions Liver failure / hepatitis: • All statins: 0.95 cases/million prescriptions • Atorvastatin: 0.61 cases/million prescriptions • Fluvastatin: 1.97 cases/million prescriptions • Lovastatin: 0.36 cases/million prescriptions • Pravastatin: 1.09 cases/million prescriptions • Rosuvastatin: 3.68 cases/million prescriptions • Simvastatin: 1.48 cases/million prescriptions Renal failure: • All statins: 0.62 cases/million prescriptions • Atorvastatin: 0.38 cases/million prescriptions • Fluvastatin: 0.68 cases/million prescriptions • Lovastatin: 0.36 cases/million prescriptions • Pravastatin: 0.41 cases/million prescriptions • Rosuvastatin: 6.83 cases/million prescriptions • Simvastatin: 0.9 cases/million prescriptions Note: no statistical comparisons made between the individual agents.	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Alsheikh-Ali et al, 2005[33] Observational, retrospective review of AERS	First year of marketing: Did not report 10/03 – 9/04: 122.9 million prescriptions	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates: • First year of marketing for the specific agent • Concurrent with first year of rosuvastatin marketing (10/1/2003 – 9/30/2004)	*First year of marketing for each agent::* • Atorvastatin, mean dose not reported (n = not reported) • Cerivastatin, mean dose not reported (n = not reported) • Pravastatin, mean dose not reported (n = not reported) • Simvastatin, mean dose not reported (n = not reported) *Concurrent with first year of rosuvastatin marketing (10/1/2003 – 9/30/2004):* • Atorvastatin, mean dose 21.8 mg/day (n = 72.9 million prescriptions filled) • Pravastatin, mean dose 18.8 mg/day (n = 15 million prescriptions filled) • Rosuvastatin, mean dose 16.7 mg/day (n = 5.2 million prescriptions filled) • Simvastatin, mean dose 53.1 mg/day (n =29.8 million prescriptions filled) Duration – not applicable, retrospective analysis.	*First year of marketing for each agent:* Serious adverse effects: More common with Cerivastatin, followed by Rosuvastatin or Simvastatin, followed by Atorvastatin or Pravastatin. Rhabdomyolysis: More common with Cerivastatin, followed by Rosuvastatin, followed by Atorvastatin, Pravastatin, or Simvastatin. Hepatic adverse events: More common with Cerivastatin, followed by Rosuvastatin or Simvastatin, followed by Atorvastatin or Pravastatin. Proteinuria: More common with Simvastatin or Rosuvastatin, followed by Pravastatin, Atorvastatin, or Cerivastatin.	*First year of agent's marketing (estimated from figure):* Combined endpoint, rhabdomyolysis, proteinuria, nephropathy, or renal failure: • Atorvastatin: 2.4 cases/million prescriptions • Cerivastatin: 76.7 cases/million prescriptions • Pravastatin: 2.8 cases/million prescriptions • Rosuvastatin: 27.6 cases/million prescriptions (p < 0.001 vs. Atorvastatin, Pravastatin, Cerivastatin) • Simvastatin: 13.4 cases/million prescriptions (NS vs. Rosuvastatin) Rhabdomyolysis: • Atorvastatin: 1.7 cases/million prescriptions • Cerivastatin: 77.8 cases/million prescriptions • Pravastatin: 0.6 cases/million prescriptions • Rosuvastatin: 16.7 cases/million prescriptions (p < 0.001 vs. all others) • Simvastatin: none Hepatic adverse events: • Atorvastatin: 6.5 cases/million prescriptions • Cerivastatin: 33.8 cases/million prescriptions • Pravastatin: 10.8 cases/million prescriptions • Rosuvastatin: 25.5 cases/million prescriptions (p < 0.001 vs. Atorvastatin, Pravastatin) • Simvastatin: 11.5 cases/million prescriptions Proteinuria: • Atorvastatin: 0.2 cases/million prescriptions • Cerivastatin: none • Pravastatin: 0.6 cases/million prescriptions • Rosuvastatin: 2.6 cases/million prescriptions (p < 0.001 vs. Atorvastatin) • Simvastatin: 4.8 cases/million prescriptions *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Alsheikh-Ali et al, 2005[33] Observational, retrospective review of AERS	First year of marketing: Did not report 10/03 – 9/04: 122.9 million prescriptions	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates: • First year of marketing for the specific agent • Concurrent with first year of rosuvastatin marketing (10/1/2003 – 9/30/2004)	*See previous page*	*First year of marketing for each agent:* Renal failure: More common with Cerivastatin or Rosuvastatin or Simvastatin, followed by Pravastatin or Atorvastatin. *Concurrent with first year of rosuvastatin marketing:* Serious adverse effects: More common with Rosuvastatin, followed by Simvastatin, Atorvastatin, or Pravastatin. Rhabdomyolysis: More common with Rosuvastatin, followed by Simvastatin, Atorvastatin, or Pravastatin. Hepatic adverse events: More common with Rosuvastatin, followed by Simvastatin, Pravastatin, or Atorvastatin.	*Continued from previous page* *First year of agent's marketing (estimated from figure):* Renal failure: • Atorvastatin: 0.7 cases/million prescriptions • Cerivastatin: 28.2 cases/million prescriptions • Pravastatin: 2.3 cases/million prescriptions • Rosuvastatin: 15.2 cases/million prescriptions ($p < 0.001$ vs. Atorvastatin, Pravastatin) • Simvastatin: 8.6 cases/million prescriptions *First year of rosuvastatin marketing:* Combined endpoint, rhabdomyolysis, proteinuria, nephropathy, or renal failure: • Atorvastatin: 315 cases, 4.3 cases/million prescriptions • Pravastatin: 52 cases, 3.5 cases/million prescriptions • Rosuvastatin: 145 cases, 27.9 cases/million prescriptions ($p < 0.001$ vs. all others) • Simvastatin: 381 cases, 12.8 cases/million prescriptions Rhabdomyolysis (estimated from figure): • Atorvastatin: 2.3 cases/million prescriptions • Pravastatin: 1.7 cases/million prescriptions • Rosuvastatin: 16.2 cases/million prescriptions ($p < 0.01$ vs. all others) • Simvastatin: 11.5 cases/million prescriptions Hepatic adverse events (estimated from figure): • Atorvastatin: 4.0 cases/million prescriptions • Pravastatin: 4.3 cases/million prescriptions • Rosuvastatin: 26.1 cases/million prescriptions ($p < 0.001$ vs. all others) • Simvastatin: 5.2 cases/million prescriptions *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Alsheikh-Ali et al, 2005[33] Observational, retrospective review of AERS	First year of marketing: Did not report 10/03 – 9/04: 122.9 million prescriptions	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates: • First year of marketing for the specific agent • Concurrent with first year of rosuvastatin marketing (10/1/2003 – 9/30/2004)	*See previous page*	*Concurrent with first year of rosuvastatin marketing:* Proteinuria: More common with Rosuvastatin, followed by Pravastatin, Simvastatin or Atorvastatin. Renal failure: More common with Rosuvastatin, followed by Simvastatin, Pravastatin, or Atorvastatin.	*Continued from previous page* *First year of rosuvastatin marketing:* Proteinuria (estimated from figure): • Atorvastatin: 0.07 cases/million prescriptions • Pravastatin: 0.3 cases/million prescriptions • Rosuvastatin: 2.7 cases/million prescriptions ($p < 0.001$ vs. all others) • Simvastatin: 0.04 cases/million prescriptions Renal failure (estimated from figure): • Atorvastatin: 1.6 cases/million prescriptions • Pravastatin: 1.9 cases/million prescriptions • Rosuvastatin: 15.0 cases/million prescriptions ($p < 0.001$ vs. all others) • Simvastatin: 5.5 cases/million prescriptions	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Cziraky et al, 2006[26] Observational, retrospective: review of a managed care organization claims database	473,343	Patients given at least 2 statin prescriptions between 7/1/2000 and 12/1/2004.	Statin monotherapy (n = 490,988 person-years): • Atorvastatin, dose not reported (n = 261,567 person-years) • Cerivastatin, dose not reported (n = 4,719 person-years) • Fluvastatin, dose not reported (n = 12,635 person-years) • Lovastatin, dose not reported (n = 26,122 person-years) • Pravastatin, dose not reported (n = 64,254 person-years) • Rosuvastatin, dose not reported (n = 8,213 person-years) • Simvastatin, dose not reported (n = 54,394 person-years) Statin plus another lipid-lowering agent (n = 11,624 person-years): • Atorvastatin, dose not reported (n = 6,544 person-years) • Cerivastatin, dose not reported (n = 25 person-years) • Fluvastatin, dose not reported (n = 226 person-years) • Lovastatin, dose not reported (n = 547 person-years) • Pravastatin, dose not reported (n = 2,241 person-years) • Rosuvastatin, dose not reported (n = 434 person-years) • Simvastatin, dose not reported (n = 1,607 person-years) Duration – not applicable, retrospective study.	*Statin monotherapy:* Myopathy: More common with Cerivastatin than other statins. Hepatic adverse events: Similar risk with any statin. Renal adverse events: More common with Simvastatin than other statins.	*Statin monotherapy:* Myopathy requiring hospitalization (ie, myoglobinuria, rhabdomyolysis, unspecified muscle disorders) • Atorvastatin: 2.45 cases/10,000 person-years • Cerivastatin: 10.59 cases/10,000 person-years ($p < 0.01$ vs. other statins) • Fluvastatin: 1.58 cases/10,000 person-years • Lovastatin: 2.3 cases/10,000 person-years • Pravastatin: 3.42 cases/10,000 person-years • Rosuvastatin: 2.44 cases/10,000 person-years • Simvastatin: 3.49 cases/10,000 person-years • No other significant differences between agents Liver events requiring hospitalization (ie, hepatic necrosis, hepatitis, other liver disorders) • Atorvastatin: 9.83 cases/10,000 person-years • Cerivastatin: 6.36 cases/10,000 person-years • Fluvastatin: 6.33 cases/10,000 person-years • Lovastatin: 6.13 cases/10,000 person-years • Pravastatin: 10.74 cases/10,000 person-years • Rosuvastatin: 8.52 cases/10,000 person-years • Simvastatin: 12.87 cases/10,000 person-years • NS between the agents Renal events requiring hospitalization (ie, acute renal failure, acute tubular necrosis, acute glomerulonephritis) • Atorvastatin: 30.97 cases/10,000 person-years • Cerivastatin: 31.78 cases/10,000 person-years • Fluvastatin: 29.28 cases/10,000 person-years • Lovastatin: 29.86 cases/10,000 person-years • Pravastatin: 31.44 cases/10,000 person-years • Rosuvastatin: 26.79 cases/10,000 person-years • Simvastatin: 54.6 cases/10,000 person-years ($p < 0.01$ vs. other agents) • No other significant differences between agents • *Results continued on next page*	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Cziraky et al, 2006[26] Observational, retrospective: review of a managed care organization claims database	473,343	Patients given at least 2 statin prescriptions between 7/1/2000 and 12/1/2004.	*See previous page*	*Statin plus another lipid-lowering agent:* Myopathy: Similar risk with any combination therapy. Hepatic adverse events: Similar risk with any combination therapy. Renal adverse events: More common with Gemfibrozil combination than with other agents.	*Continued from previous page* *Statin plus another lipid-lowering agent:* Myopathy/rhabdomyolysis requiring hospitalization • Statin + Ezetimibe: 0 cases/10,000 person-years • Statin + Fenofibrate: 5.19 cases/10,000 person-years • Statin + Gemfibrozil: 0 cases/10,000 person-years • Statin + Niacin extended-release: 3.36 cases/10,000 person-years • NS between groups Liver events requiring hospitalization • Statin + Ezetimibe: 3.44 cases/10,000 person-years • Statin + Fenofibrate: 7.78 cases/10,000 person-years • Statin + Gemfibrozil: 21.12 cases/10,000 person-years • Statin + Niacin extended-release: 6.73 cases/10,000 person-years • NS between groups Renal events requiring hospitalization • Statin + Ezetimibe: 37.89 cases/10,000 person-years • Statin + Fenofibrate: 70.05 cases/10,000 person-years • Statin + Gemfibrozil: 137.31 cases/10,000 person-years • Statin + Niacin extended-release: 23.55 cases/10,000 person-years	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Musculoskeletal Adverse Effects						
PRIMO Study, 2006[32] (Bruckert et al) Observational, retrospective: survey of patients seen by a sampling of 2,752 French general practitioners	7,924	Hyperlipidemia treated with high-dose statin in the outpatient primary care setting for at least 3 months prior to study enrollment.	Atorvastatin 40 – 80 mg/day (n = 1,844) Fluvastatin extended-release 80 mg/day (n = 3,121) Pravastatin 40 mg/day (n = 1,901) Simvastatin 40 – 80 mg/day (n = 1,027) Duration – treated for at least 3 months prior to study enrollment. Patients surveyed by physician about the presence of any muscle symptoms. Muscle symptoms included: heaviness, stiffness, cramps, weakness, and loss of strength during exercise. Study did not evaluate CPK concentrations during therapy.	Muscle symptoms: Less common with Fluvastatin extended release 80 than Pravastatin 40. Less common with Pravastatin 40 than Atorvastatin 40 – 80 or Simvastatin 40 – 80.	*Patients with Muscle Symptoms (Pravastatin used as the reference agent):* • Atorvastatin: 14.9% (OR 1.28, 95% CI 1.02 – 1.60, p = 0.035 vs. Pravastatin) • Fluvastatin: 5.1% (OR 0.33, 95% CI 0.26 – 0.42, p < 0.0001 vs. Pravastatin) • Pravastatin: 10.9% (OR 1) • Simvastatin: 18.2% (OR 1.78, 95% CI 1.39 – 2.29, p < 0.0001 vs. Pravastatin) • All agents combined: 10.5% *Patients with Muscle or Tendon Symptoms on Previous Lipid-Lowering Therapy:* • Atorvastatin: 10.7% (p < 0.05 vs. other agents) • Fluvastatin: 8.8% • Pravastatin: 8.2% • Simvastatin: 9.8% *Risk Factor for Muscle Symptoms:* • Prior symptoms with other lipid-lowering drugs: OR 10.1, 95% CI 8.23 – 12.45, p < 0.0001 • Unexplained cramps: OR 4.14, 95% CI 3.46 – 4.95, p < 0.0001 • History of elevated CPK: Or 2.04, 95% CI 1.55 – 2.68, p < 0.0001 • Family history of any muscle symptoms: OR 1.93, 95% CI 1.1 – 3.34, p = 0.022 • Family history of symptoms on lipid-lowering therapy: OR 1.89, 95% CI 1.12 – 3.17, p = 0.017 • Therapy duration greater than 3 months: OR 0.28, 95% CI 0.21 – 0.37, p < 0.0001 • Antidepressant use: OR 0.51, 95% CI 0.35 – 0.74, p = 0.0004	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Hepatic Adverse Effects						
de Denus et al, 2004[73] Meta-analysis of 13 experimental, parallel or crossover, randomized, double-blind, placebo-controlled trials[58, 84, 88, 89, 91, 93, 94, 96, 98-102]	49,275	Trials enrolling at least 400 patients; evaluating efficacy for hypercho-lesterolemia, primary prevention, or secondary prevention; excluded transplant recipients.	Statin, given at fixed or titrated dose (N = 27,276): • Fluvastatin 40 – 80 mg/day (2 trials, n = 1,058) • Lovastatin 30 – 45 mg/day (4 trials, n = 10,573) • Pravastatin 40 mg/day (5 trials, n = 13,010) • Simvastatin 27 – 30 mg/day, mean dose (2 trials, n = 2,635) Placebo (N = 21,999) Duration – 48 weeks – 6.2 years (mean 3.6 years). Did not report number of patients treated with each dose.	Abnormal LFT: Similar risk with all Statins and Placebo, Lovastatin and Placebo, Pravastatin and Placebo, Simvastatin and Placebo. Higher risk with Fluvastatin than Placebo. Note: meta-analysis did not make any statistical comparisons between the individual statins.	Patients with abnormal LFTs: *All Statins combined vs. Placebo:* • Statins: 1.14% • Placebo: 1.05% • OR 1.26, 95% CI 0.99 – 1.62, p = 0.07 *Individual Statin vs. Placebo:* • Fluvastatin: 1.13% • Placebo: 0.29% • OR 3.54, 95% CI 1.1 – 11.6, p = 0.04 • Lovastatin: 0.65% • Placebo: 0.34% • OR 1.78, 95% CI 0.8 – 3.9, p = 0.14 • Pravastatin: 1.39% • Placebo: 1.33% • OR 1.0, 95% CI 0.85 – 1.3, NS • Simvastatin: 1.86% • Placebo: 1.44% • OR 0.6, 95% CI 0.1 – 7.5, NS	1

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
Grade of Evidence. Refer to Appendix A for definitions.

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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Charles et al, 2005[75] Observational, retrospective: review of a managed care organization database	23,000	Patients receiving at least 1 statin prescription between 1/1/1997 and 12/31/2001, with ALT measured during statin therapy.	Atorvastatin 80 mg/day Cerivastatin, dose not reported Fluvastatin, dose not reported Lovastatin 20 – 80 mg/day Pravastatin, dose not reported Simvastatin 20 – 80 mg/day Duration – not applicable, retrospective study. Number of patients receiving each agent was not reported.	Increased ALT: Unable to assess comparative risk since investigators did not report number of patients receiving each agent.	Patients with ALT increased above 10 times ULN: • All cases: 0.3% (62/23,000) o Atorvastatin: 2 cases o Cerivastatin: 0 cases o Fluvastatin: 0 cases o Lovastatin: 5 cases o Pravastatin: 0 cases o Simvastatin: 0 cases • Treatment-related cases: 0.07% (16/23,000) • Cases related to interactions: 0.06% (13/23,000) Patients with ALT increase who underwent statin rechallenge (n = 10) • With same statin (7/10): symptoms recurred 3/7, symptoms did not recur 4/7 • With another statin (6/10): symptoms recurred 1/7, symptoms did not recur 5/7	3
Perger et al, 2003[74] Observational, retrospective: review of adverse event reports submitted to the World Health Organization	474.5 million prescrip-tions	Patients treated with statins in the US. Study focused on the group of patients with serious liver injury attributed to statins, based on reports submitted to the World Health Organization	Atorvastatin (n = 140.4 million prescriptions filled) Fluvastatin (n = 37.4 million prescriptions filled) Lovastatin (n = 99.2 million prescriptions filled) Pravastatin (n = 81.4 million prescriptions filled) Simvastatin (n = 116.1 million prescriptions filled) Duration – not applicable, retrospective analysis.	Fatal liver failure: Similar risk with Atorvastatin, Fluvastatin, Lovastatin, Pravastatin, and Simvastatin.	Fatal liver failure: • Atorvastatin: 0.07 cases/million prescriptions (95% CI 0.03 – 0.14) • Fluvastatin: 0.05 cases/million prescriptions (95% CI 0.006 – 0.2) • Lovastatin: 0.04 cases/million prescriptions (95% CI 0.006 – 0.09) • Pravastatin: 0.04 cases/million prescriptions (95% CI 0.007 – 0.11) • Simvastatin: 0.02 cases/million prescriptions (95% CI 0.0002 – 0.05)	3

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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Reference / Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes Results	Specific Outcomes	Grade *
Renal Adverse Effects						
Public Citizen, Review, 2004[38] Observational, retrospective review of AERS from 1/1/2001 – 8/26/2004	320.5 million prescrip-tions	Patients treated with statins in the US. Study focused on the group of patients with adverse effects during statin therapy, based on reports to AERS for the following dates: • Rosuvastatin: 9/1/2003 – 8/26/2004 • All other statins: 1/1/2001 – 9/30/2003	Rosuvastatin (n = 4.5 million prescriptions filled) All other statins (n = 316 million prescriptions filled): • Atorvastatin • Fluvastatin • Lovastatin • Pravastatin • Simvastatin Duration – not applicable, retrospective analysis.	Acute renal failure or renal insufficiency: May be more common with Rosuvastatin than other statins.	Acute renal failure or renal insufficiency, unrelated to rhabdomyolysis: • All other statins: 27 cases, or 0.085 cases/million prescriptions o Simvastatin: 0.26 cases/million prescriptions • Rosuvastatin: 29 cases, or 6.4 cases/million prescriptions (no statistical comparison reported) o Acute renal failure: 18 cases, or 4 cases/million prescriptions o Renal insufficiency: 11 cases, or 2.4 cases/million prescriptions Rhabdomyolysis: • All other statins: not reported • Rosuvastatin: 65 cases, 14.4 cases/million prescriptions	4

Abbreviations: AERS = adverse event reporting system of the Food and Drug Administration; ALT = alanine aminotransferase; CI = confidence interval; CPK = creatine phosphokinase; LFT = liver function test; N or n = number of evaluable patients in trial or treatment group; NNH = number needed to harm, or number of patients that may be safely treated before one patient experiences the adverse event; NS = not statistically significant, p value > 0.05; OR = odds ratio; ULN upper limit of normal.
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